Differential effects of antihypertensive drugs in a Bayesian perspective

Ivar Aursnes, Ingunn Fride Tvete, Jørund Gåsemyr, Bent Natvig

Department of Pharmacotherapeutics, University of Oslo, N-0316, Oslo, Norway (Prof I Aursnes MD); **Norwegian Computing Center, Oslo** (I F Tvete MS, prof B Natvig PhD); **Department of Mathematics, University of Oslo (**J Gåsemyr PhD, Prof B Natvig PhD),

Correspondence to: Prof I Aursnes

(e-mail: i.a.aursnes@ioks.uio.no)

Summary

Background According to published data, the ability to prevent various hypertension related events differs between the various anti-hypertensive drug groups. Although absolute drug effects with similar drugs also differ among the various studies, relative drug effects could be considered constant. We therefore explored the possibility of drawing statistically valid conclusions about the differences between various drug groups by doing an overview of published data.

Methods We performed a meta-analysis using a Bayesian fixed effect model in which we brought together 27 published studies. We chose to always relate the drug effects to the number of events observed with placebo drugs. We therefore obtained results both from studies reporting the effects of the newer drugs when tested against diuretics and β-blockers, and from studies in which diuretics and β-blockers had been tested against placebo. We constructed the posterior probability distributions of the relative effects of ACE-inhibitors versus calcium antagonists with three different endpoints: stroke, coronary disease and heart failure. We then calculated point estimates of effects with 95% credibility intervals. As an intermediate step in this procedure we obtained similar information about the effects of the three groups of active drugs, ACE-inhibitors, calcium antagonists and diuretics or β-blockers, tested against placebo.

Findings ACE-inhibitors and calcium antagonists have an almost identical ability to prevent stroke in hypertensive individuals with a risk ratio (RR) of 1.04. On the other hand, calcium antagonists reduce coronary disease by only 9% relative to placebo. When ACE-inhibitors and calcium antagonists are compared by the Bayesian method, the outcome is a 14% difference in

favour of the ACE-inhibitors to prevent coronary disease, with a credibility interval reaching identity. Nor do calcium antagonists do as well as diuretics or β-blockers in this respect, RR = 1.11 with 95% credibility interval 1.01 to 1.22. All the tested drug groups have a profound preventive effect on the occurrence of heart failure when given to hypertensive patients, showing reductions of 44% to 56%. When ACE-inhibitors are compared with calcium antagonists the risk ratio is 0.79, with a credibility interval 0.65 to 0.95.

Interpretation The conclusion of our analysis is a statistically significant difference between ACE-inhibitors and calcium antagonists in respect of effects on coronary disease and heart failure when treating hypertensive individuals, ACE-inhibitors being more efficacious. The difference is modest and both drug groups are acceptable as first line treatments together with diuretics and β-blockers. There are no differences in the effect on stroke.

Introduction

A series of publications between 1974 and 1994 established a positive effect of drug treatment on the clinical course in hypertensive patients. In these studies, diuretics or β-blockers were the first choice in the treatment groups.[1] These drugs were tested against placebo or “usual care” in the control groups. Later studies, published from 1995 onwards, have been summarized prospectively and a report has recently appeared in the Lancet.[2] In many of these studies on the more modern drugs, the control groups were assigned β-blockers or diuretics, since, at that time, giving no treatment was considered un-ethical, even in patients with only moderate hypertension.

These data can be used to explore whether the ability to prevent various hypertension-related events differs for the various newer drugs. A prerequisite is that the drug effects in the control groups given β-blockers or diuretics are constant. Although one would expect absolute treatment effects to be related to the risk of morbidity in the population under study, the relative effects could be constant.

We therefore examined the relationship between clinical outcome and basal risk level for various categories of events in studies on the traditional anti-hypertensives. To the extent that the relative drug effects could be considered constant, we drew conclusions from an overview of published data on the newer drugs. We used a Bayesian statistical approach, focusing on differences between the drug groups.

Methods

Our main question was whether there are different effects of treatments with ACE-inhibitors and calcium antagonists in patients with hypertension. We chose to study the effects on the occurrence of stroke, coronary disease and heart failure separately. We prepared an overview using a Bayesian fixed effect model similar to the one described in Aursnes et al 2000.[3] For simulating from the distributions in the present paper we have used the program package WinBUGS available free of charge at http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml. The main difference was that, on that occasion, when studying patients with osteoporosis, we combined only four studies at a time, whereas we now brought together up to 27 studies. Some of the studies were quite small. Near homogeneity was obtained by doing calculations on relative effects only. Thus, as opposed to absolute effects, for instance differences in number of events per year in drug groups versus control groups, we used the corresponding ratio between the two.

We chose to always relate the drug effects to the number of events observed with placebo drugs. We could achieve this with our model, even when only about half the eligible studies included placebo-treated groups. Therefore all effect ratios (relative risks) reported are founded on all the studies, unless otherwise stated in Results. We excluded a few of the studies in our primary analysis, however, in order to further address the question of heterogeneity in the study material. For purposes of demonstration, we included results from all eligible studies in the calculations.

Primary data

Data were gathered from two sources. The first source was a meta-analysis of studies that have been published since 1995 on the effect of anti-hypertensive drugs on clinical outcomes.[2] From that meta-analysis we selected studies on ACE-inhibitors and calcium antagonists tested against each other, against placebo or against diuretics and β-blockers. Among the various study endpoints recorded we chose the effects on stroke, coronary disease and heart failure. Other endpoints, like total death, will necessarily be a sum of the effects in all these categories. We found 14 eligible studies,[4,5,6,7,8,9,10,11,12,13,14,15,16,17] of which two studies contained no data on heart failure.[6,7] In four of the studies hypertension was not one of the inclusion criteria.[4,5,6,7] Although many of the patients were hypertensive, the average blood pressures were 123-139/74-79 mmHg. We therefore excluded these studies in our primary analysis. The same applied to the CAPPP study.[10] This was a randomized study on an ACE-inhibitor in hypertensive individuals, but the blood pressure levels were higher in the treatment group than in controls at the start of study, indicating faulty randomization.

The second source of data comprised reports from studies in which diuretics and β-blockers were tested against no treatment. We chose studies including patients with diastolic blood pressures up to 115 mmHg. This was the inclusion criterion used by The Swedish Council on

Technology in Health Care, and a list of such studies was published in June 1994 with tables in English.[1] Of the 14 studies listed there,[18,19,20,21,22,23,24,25,26,27,28,29,30,31] one dealt with several drug groups[31] and was omitted by us, whereas in the others diuretics was the first choice drug, often in combination with β-blockers. We used only strata I-II in the HDFP-study[22] which fulfilled our inclusion criterion for blood pressure. We included all patients in EWPHE [26] although some patients had diastolic blood pressures up to 119, but others had pressures down to 90 mmHg. We observed that the meta-analysis by Collins et al,[32] included another three studies not included by us. Among those, one did not include diuretics,[33] one had methyldopa as an alternative first choice,[34] and one accepted only diastolic blood pressures above 110 mmHg at start of study.[35] We thus ended up with altogether 13 eligible studies in this group. Notably, none of these included data on heart failure.

The mentioned meta-analysis published in 2000 included all studies published in 1995 and later.[2] It did not include any studies in which older drugs like diuretics or β-blockers were compared with no treatment. Since the Swedish report[1] was published in 1995, we also searched Medline for the year 1994 to see whether any publications had been left out, but did not find any.

The model

Let us now consider one particular kind of drug and one specific endpoint. Assume that there are n studies on the effects of this kind of drug given this endpoint. When considering the effects of diuretics or β-blockers on stroke or coronary disease, n = 21. For i = 1,……,n let

$p_{1,i}$ = the probability of at least one occurrence of the specific endpoint for an arbitrary patient in the course of the study period of the i^{th} study when placebo is used

$p_{2,i}$ = the probability of at least one occurrence of the specific endpoint for an arbitrary patient in the course of the study period of the i^{th} study when the particular kind of drug is used

$X_{1,i}$ = the number of patients with at least one occurrence of the specific endpoint in the course of the study period of the i^{th} study when placebo is used

$X_{2,i}$ = the number of patients with at least one occurrence of the specific endpoint in the course of the study period of the i^{th} study when the particular kind of drug is used

$m_{1,i}$ = the number of patients in the i^{th} study in the placebo group

$m_{2,i}$ = the number of patients in the i^{th} study in the particular drug group

We assume $X_{1,i} \sim Bin(m_{1,i}, p_{1,i})$ while $X_{2,i} \sim Bin(m_{2,i}, p_{2,i})$ and that all variables are independent. Furthermore, we assume that the multiplicative treatment effect γ (the risk ratio) for the particular kind of drug and the specific endpoint is constant in all n studies, regardless of prevalence and length of study period, i.e.

$$\gamma = p_{2,i} / p_{1,i}, \qquad i=1,.....,n$$

Therefore, in practice, we will have only n+1 free parameters $p_{1,i}$ i=1,.....,n and γ.

Probability distributions describing our initial uncertainty are called prior distributions (that is, before the data are collected). Here we assume that the prior distributions for $p_{1,i}$ i=1,.....,n and γ are independent and uniform over the interval [0,1]. This corresponds to omitting information on $p_{1,i}$, i=1,.....,n and assuming that the effect of the particular kind of drug is at least as good as the effect of placebo.

Denote γ^a, γ^b, and γ^c the risk ratio corresponding respectively to ACE-inhibitors, diuretics or β-blockers and calcium antagonists. The risk ratio of ACE-inhibitors to calcium antagonists $\alpha^{a/c}$ is then expressed by

$$\alpha^{a/c} = \gamma^a/\gamma^c ,$$

and that of calcium antagonists to diuretics or β-blockers $\alpha^{c/b}$ by

$$\alpha^{c/b} = \gamma^c/\gamma^b .$$

We constructed the posterior probability distributions of the relative effects of ACE-inhibitors versus calcium antagonists with tree different endpoints: stroke, coronary disease and heart failure. We then calculated point estimates of effects with 95% credibility intervals. As an intermediate step in this procedure we obtained similar information on the effects of the three active groups of drugs, ACE-inhibitors, calcium antagonists and diuretics or β-blockers, tested against placebo.

Further analysis

For purposes of comparison, we also calculated the differences in effects of ACE-inhibitors and calcium antagonists by only using the results from the two studies that had compared these two drugs directly.[17,8] For that purpose we used the same model as the one described above.

To further elucidate possible inhomogeneity in effects between various studies of diuretics or β-blockers against placebo, we calculated basal annual risks in the various populations under study and plotted these against the effects reported in the same studies. We were able to do this both with stroke and with coronary disease as endpoint.

Results

ACE-inhibitors and calcium antagonists have an almost identical ability to prevent stroke in hypertensive individuals (figure 1). This is the result of the full analysis showing a risk ratio (RR) of 1.04, and also of the calculation that included only the studies ABCD[17] and STOP-2[8] (RR=1.02) in which a direct comparison between these two drug groups was performed. Notably the result of our calculation, including the credibility interval for the second ratio, is identical to the result obtained with a non-Bayesian method presented by others.[2] When we include studies not directly aimed at hypertensive individuals and a study without proper randomization, the RR deviates from unity (figure 1). The same figure also shows that the three different drug groups all reduce the stroke risk by 37 to 45% relative to placebo.

As opposed to the effect on stroke, the effects on the occurrence of coronary disease in patients with hypertension differ for the various drugs (figure 2). The effects are quite similar for ACE-inhibitors and for the group diuretics or β-blockers, a 22% and 18% reduction respectively, relative to placebo. Calcium antagonists reduce coronary disease by 9% only. When this difference between ACE-inhibitors and calcium antagonists was analysed using our Bayesian approach the outcome was a 14% difference, with a credibility interval reaching identity. Figure 2 also shows that a direct comparison of ACE-inhibitors and calcium antagonists estimates the former group to be 19% more effective. When the studies HOPE[4], PART2[5], QUIET[6] and SCAT,[7] which are not hypertension studies were included, and even CAPPP[13] with its faulty randomisation, the relative risk did not change substantially.

Somewhat surprising was the result shown in figure 2 that diuretics or β-blockers have a better effect than calcium antagonists do on the occurrence of coronary disease in hypertensives. Formally tested the risk ratio is 1.11, with a 95% credibility interval of 1.01 to 1.22.

The existing data on heart failure are collected in figure 3. All the tested drug groups have a profound preventive effect on the occurrence of heart failure when given to hypertensive patients, showing reductions of 44% to 56%. Using 11 out of the 14 studies listed in figure 3, the risk ratio of ACE-inhibitors against calcium antagonists is 0.79 with a credibility interval of 0.65 to 0.95. The ratio hardly changes when CAPPP is also included in the calculation, whereas the outcome did change when HOPE and PART2 were put together with the other studies.

The far right-hand columns in figures 1 to 3 give the annual risk of events of various kinds in the populations under study. We transferred data from figures 1 and 2 on effects of diuretics or β-blockers tested against placebo to figure 4, where the calculated treatment effects for each of the studies are plotted against the annual risks in the control population. The plot shows that the approximately 40% risk reduction for stroke is fairly constant through all degrees of basal risk. On the contrary, the effect of the treatment on coronary disease is positively correlated with risk. When the annual risk of coronary disease exceeds 2%, the effect on coronary disease is comparable to the effect on stroke. In low risk hypertensives, on the other hand, drug treatment seems to have a deleterious effect on coronary disease. Notably, the figure also shows that in hypertensive individuals, or at least in those included in clinical trials, the risk of stroke is just as high as the risk of coronary disease, whereas in normotensive populations of similar age we know that coronary disease is far more prevalent than stroke.

Discussion

With all clinical evidence included, we found a 37-45% reduction in the risk of stroke when hypertensive individuals are treated with various groups of drugs. Thus, given this endpoint, no differences are observed between ACE-inhibitors, calcium antagonists and a combined group of

diuretics and beta-blockers. Since we used the combined group as a point of reference in our calculations, we assumed that differences in effects obtained within this group were determined by chance only. Fortunately, as seen from figure 4, the effects on stroke are constant across various levels of underlying risk in the population. Notably, a similar conclusion as to differential effects can be drawn from the analysis including two studies only, see figure 1, which shows the same effect of ACE-inhibitors and calcium antagonists, a result almost identical to the one obtained from the calculation where 22 studies were included.

Our conclusions are much weaker when it comes to the effects on coronary disease. All the same, the conclusion from the combination of two studies (see figure 2) that the ACE-inhibitors are more efficacious than calcium antagonists, is supported by the full calculation with all studies included. So, despite the result shown in figure 4 that the effect of diuretics and beta-blockers is dependent on the underlying risk, this conclusion may be correct. One likely explanation is that other drug groups, if they had been tested directly against placebo, would show the same association with underlying risk. Indeed, in one instance such a test was performed. In the TOMHS study,[31] various drug groups were tested against placebo in patients with particularly low risk. The treated fared less well than the untreated, but the number of events was too low to draw firm conclusions. All in all, we believe that the preventive effect of calcium antagonists on the risk of coronary disease is both statistically and clinically less than both the effect of ACE-inhibitors and of diuretics or β-blockers.

Similarly one cannot completely dismiss the possibility that the effects of diuretics or β-blockers on heart failure vary more than can be put down to chance, which would invalidate our conclusion. With our fixed effect model it is assumed that this is not the case. Notably, all three drug groups had a profound beneficial effect on this outcome. There are some differences, however, and the conclusion of our analysis is a statistically significant difference between ACE-

inhibitors and calcium antagonists, with consistent results from both the two and from the 14 studies brought together.

The clinical significance of our all over result is less clear, but it is easy to conclude, as others have done before, that stroke can be prevented effectively by using the less expensive diuretics and β-blockers.[36] Furthermore, there is no possibility to choose between ACE-inhibitors and calcium antagonists when a secondary drug is needed and prevention of stroke is in mind.

A question mark is attached to coronary disease. It has been suggested that calcium antagonists are deleterious to patients with acute coronary occlusions, but the warning has usually referred to short-acting drugs of the dihydropyridine type. The studies included in our analysis referred mainly to long acting variants and were directed at the preventive effects of the drugs on manifestation of coronary disease. However, a modest reduction of 9% is observed for calcium antagonists relative to placebo, significantly less than for both ACE-inhibitors and diuretics or β-blockers. Together with the observation that hypertensive individuals with low risk of coronary disease become worse when treated, and because it is hard to tell which people host a beginning coronary sclerosis, a modest demand would be that calcium antagonists should be withdrawn from the first line armament of drugs for the mildest forms of hypertension.

We think we have made interesting observations by successively excluding and including the HOPE study in our analysis. Since this is a large study dealing with an ACE-inhibitor it has a potentially large effect on the risk in the meta-analysis relative to calcium antagonists. The inclusion of this study, together with the PART 2 study which also included patients who were normotensive, diminished the difference between the two drug groups when the endpoint was heart failure. A likely explanation is that ACE-inhibitors prevent heart failure by lowering the blood pressure only. Other effects, like diminishing the size of infarctions, have also been suggested for this drug group.[37]

We do not know to what extent our fixed effect model holds true in respect of heart failure. This outcome will be important in an ongoing study,[38] of which one arm already has been discontinued because the test drug, an α-blocker, was linked to increased frequency of heart failure. Further results from this and other future studies will change our database. Fortunately, the Bayesian model can easily be updated when new data are forthcoming. In the meantime patients must be treated according to the best knowledge available so far.

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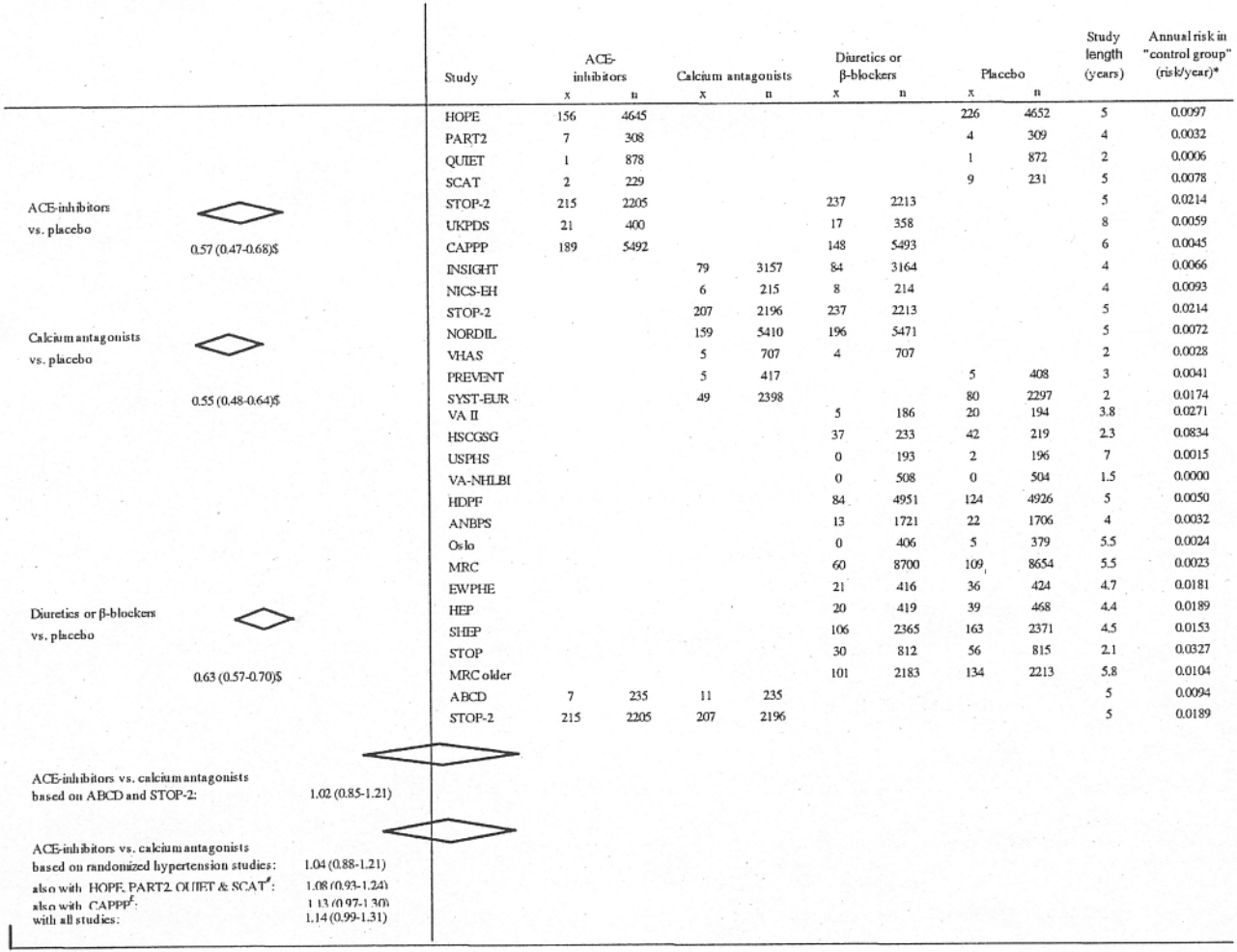
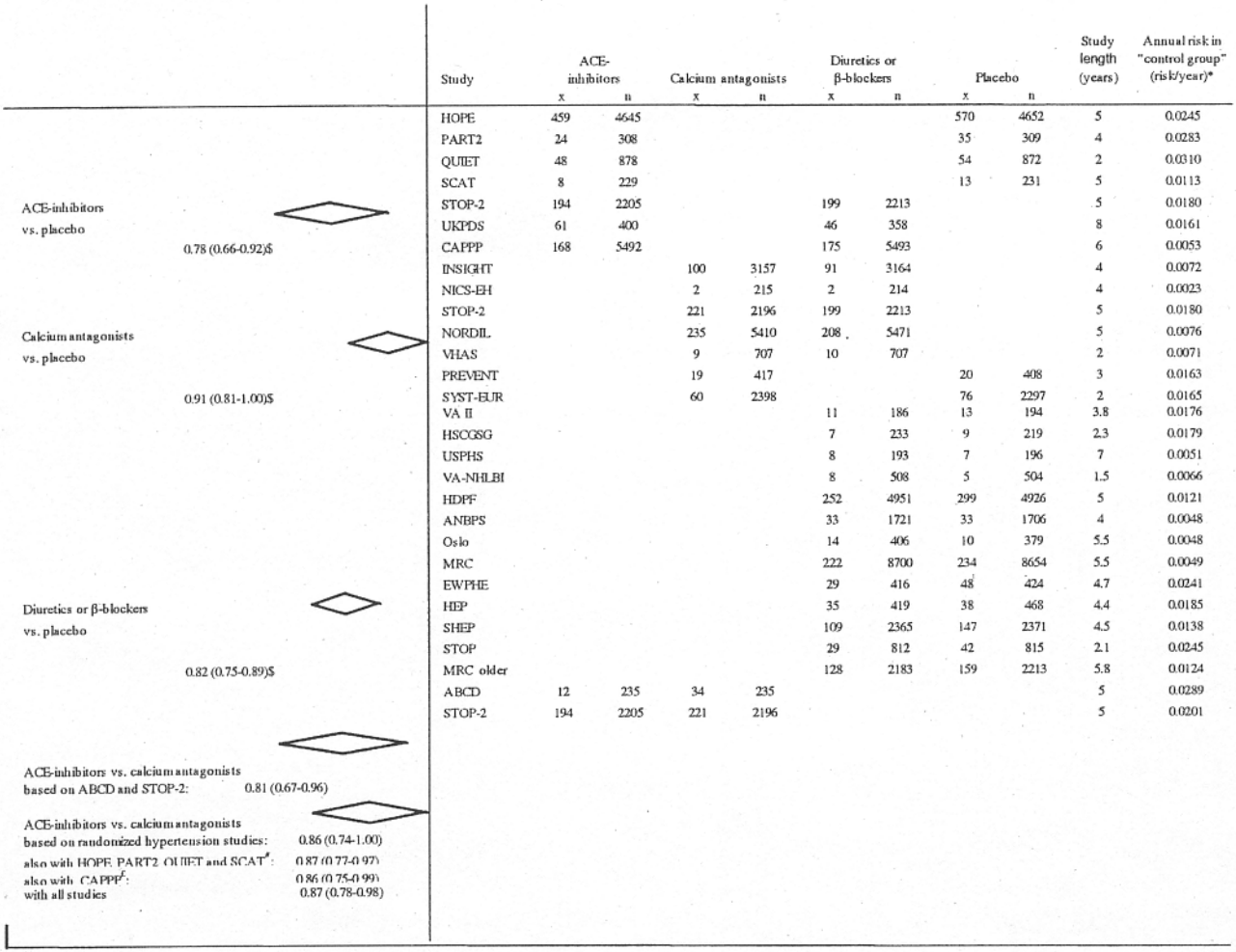
Figure 1: Comparison of effects on stroke



Study	ACE-inhibitors x	ACE-inhibitors n	Calcium antagonists x	Calcium antagonists n	Diuretics or β-blockers x	Diuretics or β-blockers n	Placebo x	Placebo n	Study length (years)	Annual risk in "control group" (risk/year)*
HOPE	156	4645					226	4652	5	0.0097
PART2	7	308					4	309	4	0.0032
QUIET	1	878					1	872	2	0.0006
SCAT	2	229					9	231	5	0.0078
STOP-2	215	2205			237	2213			5	0.0214
UKPDS	21	400			17	358			8	0.0059
CAPPP	189	5492			148	5493			6	0.0045
INSIGHT			79	3157	84	3164			4	0.0066
NICS-EH			6	215	8	214			4	0.0093
STOP-2			207	2196	237	2213			5	0.0214
NORDIL			159	5410	196	5471			5	0.0072
VHAS			5	707	4	707			2	0.0028
PREVENT			5	417			5	408	3	0.0041
SYST-EUR			49	2398			80	2297	2	0.0174
VA II					5	186	20	194	3.8	0.0271
HSCGSG					37	233	42	219	2.3	0.0834
USPHS					0	193	2	196	7	0.0015
VA-NHLBI					0	508	0	504	1.5	0.0000
HDPF					84	4951	124	4926	5	0.0050
ANBPS					13	1721	22	1706	4	0.0032
Oslo					0	406	5	379	5.5	0.0024
MRC					60	8700	109	8654	5.5	0.0023
EWPHE					21	416	36	424	4.7	0.0181
HEP					20	419	39	468	4.4	0.0189
SHEP					106	2365	163	2371	4.5	0.0153
STOP					30	812	56	815	2.1	0.0327
MRC older					101	2183	134	2213	5.8	0.0104
ABCD	7	235	11	235					5	0.0094
STOP-2	215	2205	207	2196					5	0.0189

* groups to the right considered as controls
$ without CAPPP, HOPE, PART2, QUIET and SCAT
# not hypertension studies
£ not properly randomised

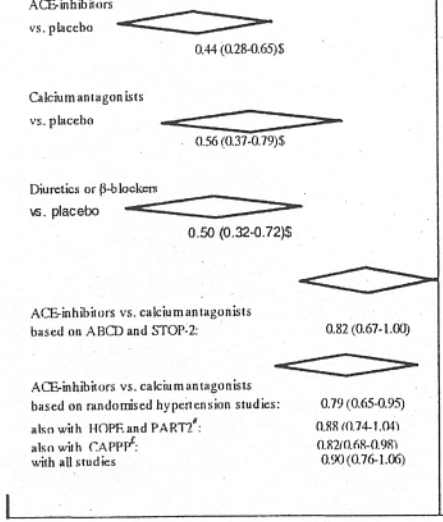
Figure 2: Comparison of effects on coronary disease



Study	ACE-inhibitors x	ACE-inhibitors n	Calcium antagonists x	Calcium antagonists n	Diuretics or β-blockers x	Diuretics or β-blockers n	Placebo x	Placebo n	Study length (years)	Annual risk in "control group" (risk/year)*
HOPE	459	4645					570	4652	5	0.0245
PART2	24	308					35	309	4	0.0283
QUIET	48	878					54	872	2	0.0310
SCAT	8	229					13	231	5	0.0113
STOP-2	194	2205			199	2213			5	0.0180
UKPDS	61	400			46	358			8	0.0161
CAPPP	168	5492			175	5493			6	0.0053
INSIGHT			100	3157	91	3164			4	0.0072
NICS-EH			2	215	2	214			4	0.0023
STOP-2			221	2196	199	2213			5	0.0180
NORDIL			235	5410	208	5471			5	0.0076
VHAS			9	707	10	707			2	0.0071
PREVENT			19	417			20	408	3	0.0163
SYST-EUR			60	2398			76	2297	2	0.0165
VA II					11	186	13	194	3.8	0.0176
HSCGSG					7	233	9	219	2.3	0.0179
USPHS					8	193	7	196	7	0.0051
VA-NHLBI					8	508	5	504	1.5	0.0066
HDPF					252	4951	299	4926	5	0.0121
ANBPS					33	1721	33	1706	4	0.0048
Oslo					14	406	10	379	5.5	0.0048
MRC					222	8700	234	8654	5.5	0.0049
EWPHE					29	416	48	424	4.7	0.0241
HEP					35	419	38	468	4.4	0.0185
SHEP					109	2365	147	2371	4.5	0.0138
STOP					29	812	42	815	2.1	0.0245
MRC older					128	2183	159	2213	5.8	0.0124
ABCD	12	235	34	235					5	0.0289
STOP-2	194	2205	221	2196					5	0.0201

* groups to the right considered as controls
$ without CAPPP, HOPE, PART2, QUIET and SCAT
# not hypertension studies
£ not properly randomised

Figure 3: Comparison of effects on heart failure



Study	ACE-inhibitors x	ACE-inhibitors n	Calcium antagonists x	Calcium antagonists n	Diuretics or β-blockers x	Diuretics or β-blockers n	Placebo x	Placebo n	Study length (years)	Annual risk in "control group" (risk/year)*
HOPE	147	4645					173	4652	5	0.0074
PART2	7	308					10	309	4	0.0081
STOP-2	149	2205			177	2213			5	0.0160
UKPDS	7	400			7	358			8	0.0024
CAPPP	75	5492			66	5493			6	0.0020
INSIGHT			28	3157	16	3164			4	0.0013
NICS-EH			0	215	3	214			4	0.0035
STOP-2			186	2196	177	2213			5	0.0160
NORDIL			63	5410	54	5471			5	0.0020
VHAS			1	707	0	707			2	0.0000
PREVENT			1	417			5	408	3	0.0041
SYST-EUR			40	2398			51	2297	2	0.0111
ABCD	10	235	8	235					5	0.0068
STOP-2	149	2205	186	2196					5	0.0169

0 1.0
Relative risk

* groups to the right considered as controls
$ without CAPPP, HOPE and PART2
# not hypertension studies
£ not properly randomised

Figure 4: Annual risks and treatment effects in studies on diuretics or β-blockers versus placebo